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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YU, MISOOK	
ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/881,636	FARIS ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *seq. alignment* .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group I, drawn to %%P4H4-related protein and variants in Paper No. 11 is acknowledged. Claims 56-69 are pending and examined on merits.

Specification

The disclosure is objected to because it contains for example, page 5 line 5 and numerous other places throughout the specification, an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. fixed

Claim Objections

Claim 64 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 64 depends on claim 63 drawn to a protein comprising fragments of SEQ ID NO:2 but claim 64 is drawn to a peptide comprising fragments other than SEQ ID NO:2. moot

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 56-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 56, 57, and 59-62 recites "Figure 2 (SEQ ID NO:2)" but it is not clear what the metes and bounds are for the limitation. Figure 2 and SEQ ID NO:2 do not contain a same protein sequence. For purpose of this office action, the examiner will assume

that Claims 56, 57, and 59-6 are drawn to SEQ ID NO:2. However, this treatment does not relieve applicant the burden of responding to this rejection.

Claims 57, 58, and 64 recite "conservative substitution" but it is not clear what the metes and bounds are for the limitation.

Claim 67 recites "stringent conditions" but it is not clear what the metes and bounds are for the limitation. The specification at page10 lines 11-29 does not define the recited limitation.

Claim 68 recites "a peptide region of at least 5 amino acids of Figure 2 in any whole number increment up to the end of said peptide of Figure 2" but it is not clear what the metes and bounds are for the limitation. For the purpose of the office action, the examiner will assume that the instant claim 68 claims at least 5 contiguous amino acids of SEQ IF NO:2 because the numbering scheme at Figs.11-14 seem to indicate that amino acids numbering is based on SEQ ID NO:2. However, this treatment does not relieve applicant the burden of responding to this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56-58, 66, and 67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to **enable** one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 56-58, 66, and 67 recite specific biological material designated as p55P4H4-EBB12.

It is apparent that the recited plasmid is required to practice the claimed invention, because they are specifically required in the claims. As required elements they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first

paragraph, may be satisfied by a deposit of the plasmid listed in claim 7. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the plasmid in the claim, and they do not appear to be readily available material. Deposit of the plasmid would satisfy the enablement requirements of 35 U.S.C. 112. While the claims have deposit numbers, the specification does not indicate the terms of the deposit.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Claims rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession** of the claimed invention. Since the specification at page 21 lines 29 and 30 says that naturally occurring allelic variants are 90% or more homologous, claims 57-62, 64, 66-69 are interpreted as drawn to **a genus** of proteins recited as a 55P4H4-related protein defined in terms of degree of differences in amino acids composition and length from SEQ ID NO:2. The specification provides evidence for SEQ ID NO:2 only. Based on one species, one cannot predict the types of additional species. Since the genus includes a large number of unpredictable species, possession of only one species is not seen as sufficient to reasonably convey possession of the entire genus. It is concluded that applicants adequately SEQ ID NO:2.

Claims 56-69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to **enable** one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or **use** the invention. The claims are interpreted as drawn to SEQ NO:2 and its fragments of various lengths. The specification at pages 28 and 29 asserts that the instant invention could be used in cancer diagnosis and cancer treatment. The factors which must be considered in determining undue experimentations are set forth in In re Wands USPOQ2d 1400. The factors include 1) quantity of experimentation necessary, 2) the amount of guidance presented, 3) the presence or absence of working example, 4) the nature of the invention, 5) the state of the prior art, 6) the predictability of the art, 7) breath of the claims. The nature of the instant invention is SEQ ID NO:2 is a human protein with an unknown biological and biochemical function. The specification discloses: Figs. 4-17 using Northern analysis show mRNA encoding the instant

invention is expressed in some normal human tissues, some cancerous tissues, especially Fig. 9 shows that both normal and prostate cancer tissues expresses the mRNA; Tables V –XVIII show estimated half time of dissociated analysis of HLA peptide scoring of various 9-mers of instant invention.

One cannot extrapolate the teaching of the specification to the claimed invention because the specification does not teach that the claimed peptides could be used as cancer vaccine to generate instantly claimed protein specific CTLs in vivo. The specification fails to teach how administration of the claimed peptide would produce a sufficient amount of CTLs to kill tumors in an animal or human that has malignant cells expressing the instantly claimed protein. The specification at Fig. 6 suggests that the protein might be expressed in normal tissue, i.e. a self-protein and that self-tolerance may eliminate T cells that are capable of recognizing these epitopes with high avidity (Sherman, LA et al, 1998, Critical reviews in Immunol, 18(1-2): 47-54, see especially at the abstract and Table 2). In other words, only CTLs with low affinity are left, which may not be optimal for tumor elimination *in vivo*. One of the problem is that after some period of time in the presence of tumor cells, T cells may lose their functional activity.

In addition, one cannot extrapolate the teaching of the specification to the claimed invention because the specification provides no exemplification of or guidance on how to use the claimed vaccine formulation or antigen for active immunotherapy in humans. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10: 1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're

likely to get the following response: cancer vaccines don't work. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1). Furthermore, Boon (Adv Can Res, 1992, 58:177-210) teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph).

Moreover, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para of column 1). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the

claimed peptide would be useful for treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

In addition, anti-tumor agents and those that prevent, reduce, retard or eliminate secretion of metastatic promoters, must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor or metastatic promotor-producing cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established.

The specification suggests that the instant invention could be used as a cancer biomarker because the mRNA level is over-expressed in some cancer cells especially lung cancer in Figure 17. One cannot extrapolate the teaching of the specification to the enablement of the claimed invention because there is no teaching of whether any protein product is actually produced from the mRNA transcripts. The art recognizes that expression of mRNA, does not dictate nor predict the translation of such mRNA into a

polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. For the above reasons, one of skill in the art would not be able to predict any protein is expressed from the mutant Fhit transcript.

One cannot extrapolate the teachings of the specification to the claimed invention because the specification provides neither guidance on nor exemplification of how to correlate the data presented in the specification with the ability to use SEQ ID NO:2 for the assessment of cancer risk. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of tumorigenicity have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (p. 2713s, col 1). The

reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2).

Further, one cannot extrapolate the teaching of the specification to the claimed invention because the specification does not teach that method of positively correlating tumor cell growth *in vivo* to either detection of SEQ ID NO:2 because the characteristics of cultured cell lines generally differ significantly from the characteristics of in vivo primary cancers or metastatic cancers. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary - type step that enables the new line to thrive in its artificial environment. This step

transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on the cell culture data presented in the specification, it could not be predicted that the proteolytic fragments could be detected in blood or cell surface *in vivo*.

The specification provides insufficient guidance, and provides no working examples of correlating in vivo tumor growth to detection of SEQ ID NO;2, which would provide guidance to one skilled in the art to use the claimed invention without undue experimentation. Considering lack of examples and the limited teachings of the specification, and unpredictability in the art, it is concluded that undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 68 and 69 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat. 6,235,679 (filing date of 05-27-1998).

Claims 68 and 69 are interpreted as drawn to peptides comprising at least 5 consecutive amino acids of SEQ ID NO:2 with an amino acid position having a value greater than 0.5 in the hydrophilicity profile of Figure 11.

US Pat. 6,235,679 teaches a peptide comprising ISELL corresponding amino acids #16-20 of the instant SEQ ID NO:2 with a value greater than 0.5 in the hydrophilicity profile of Figure 11. Note sequence alignment.

Thus, US Pat. 6,235,679 anticipates the instant claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800 1600

Misook Yu
December 3, 2002